IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Endectomectin 10 mg/ml Solution for Injection for Cattle, Sheep and Pigs

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Endectomectin 10 mg/ml Solution for Injection for Cattle, Sheep and Pigs
Active substance	Ivermectin
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP
Legal basis of application	The application was made in accordance with Article 13(a)(iii) of Directive 2001/82/EC, on the basis of essential similarity
Date of Authorisation	12th June 2009
Target species	Cattle, sheep and pigs
Indication for use	Endectoparasiticide
ATCvet code	QP54AA01 Ivermectin

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II QUALITY ASPECTS

The product contains the active substance ivermectin (10 mg/ml) and the excipients glycerol formal and polyethylene glycol.

The container/closure system consists of high density polyethylene vials of 50 ml, 100 ml, 250 ml, 500 ml and 1 L with bromobutyl bungs and aluminium caps.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is ivermectin, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on Intermediate Products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

The application was made in accordance with Article 13(a)(iii) of Directive 2001/82/EC, on the basis of essential similarity and therefore basic pharmacological and toxicological data relating to the active substance are not required.

The Applicant has conducted bioequivalence studies and target animal tolerance studies with the candidate product in the proposed target species.

The pharmacokinetic profile of the final formulation has been characterised in each of the target species and is considered to be broadly similar to that of the reference product. It is accepted that bioequivalence has been demonstrated following a single subcutaneous administration of the test and reference products.

With respect to user safety, the following is noted:
• Ivermectin has a relatively low order of toxicity in mammalian species.
• The potential for sensitisation and irritancy is low.
• Ivermectin is used therapeutically in humans with little, if any, risk at normal doses (100-200 μg/kg).
• The excipients included in the test product are widely used in veterinary medicines and human medicines and are generally considered to have an acceptable level of safety. They are listed in Annex II of Council Regulation 2377/90.
• The most likely routes of operator exposure would be contamination of hands and possible oral exposure via contaminated hands. The warning statements included on the SPC are appropriate: “Do not smoke, eat or drink while handling the product. Wash hands after use.”
• Local irritation and/or pain may result from inadvertent self-injection. An appropriate warning statement is included on the SPC.
• The current application was made in accordance with Article 13(a)(iii) of Directive 2001/82/EC, on the basis of essential similarity, and the user risks associated with the use of this product are likely to be similar to those associated with the use of the reference product. The user safety statements included on the SPC and product labelling for the test product are in keeping with those authorised for the reference product.

In conclusion, the user risks associated with the use of this product are considered to be minimal. However, given the potential for inadvertent skin and oral exposure, the proposed user warning statements are considered appropriate.

Based on the information provided, it is accepted that this product, when used in accordance with label recommendations, is unlikely to be an unacceptable risk to the environment.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.B Residues Documentation

Precise Identification of the Product concerned by the Application

Active substance
Ivermectin 1 % w/v

Excipients
Propylene glycol
Glycerol formal

Residue Studies

Confirmatory residue studies were conducted in cattle sheep and pigs. All studies were conducted to GLP and were of an adequate quality for determination of meat withdrawal periods.

MRLs

Ivermectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All mammalian food-producing species
Muscle	30 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg
Fat	100 µg/kg

Marker residue: Ivermectin H_2B1_a

Withdrawal Periods

The proposed withdrawal periods of 42 days for sheep and 28 days for pigs are justified based on the confirmatory residue studies provided. Following a Commission Decision in respect of an Article 35 referral relating to marketing authorisations for veterinary medicinal products which contain the active substance ivermectin, the withdrawal period for cattle was changed to 49 days.
In accordance with Commission Regulation (EU) No 37/2010, ivermectin is contraindicated for use in animals producing milk intended for human consumption and in accordance with current recommendations a withdrawal time of 60 days for dairy cattle and sheep applies.

Analytical Methods used

Marker residue: Ivermectin H_2Bl_a
Analytical method: HPLC, followed by fluorescence detection. Quantification is by measurement of the sample peak response in comparison to an internal standard peak response. The peak height ratio is compared with a standard line prepared from spiked plasma of known concentration.

The method was validated in line with existing guidance.

IV CLINICAL ASSESSMENT (EFFICACY)

The application was made in accordance with Article 13(a)(iii) of Directive 2001/82/EC, on the basis of essential similarity.

Data provided in support of the application show that the test product (Endectomectin Injection) when administered at the recommended treatment dose on a single occasion to cattle, sheep and pigs is bioequivalent to the reference product (Ivomec Classic Injection for Cattle and Sheep; Ivomec Injection for Pigs); consequently, it can be concluded that, for each of the target species, the systemic effects of the two products in respect of safety and efficacy will be the same following a single administration.

The proposed posology indicates that Endectomectin Injection should be administered to sheep on two occasions at an interval of 7 days for effective treatment of *Psoroptes ovis*. Given that bioequivalence following the second administration of the test product was not proven, the Applicant conducted a study to confirm efficacy of the test product against *Psoroptes ovis* thereby providing the necessary assurance relating to efficacy against this claimed target parasite.

To further support the safety of the final formulation, the Applicant provided the results of study that demonstrate that the product is well tolerated systemically when administered at multiples of the recommended treatment dose to cattle, sheep and pigs. Local injection site reactions were recorded; typically, these are mild and resolve within 1 to 4 weeks of product administration.

The proposed SPC (in terms of indications/recommendations for use and target animal safety statements) reflects the authorised SPC of the reference products (Ivomec Classic Injection for Cattle and Sheep; Ivomec Injection for Pigs).

V OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:

Summary of change	Approval date
Change in the cattle meat withdrawal period following a Commission Decision in respect of an Article 35 referral relating to marketing authorisations for veterinary medicinal products which contain the active substance ‘ivermectin’. (CRN 7007174)	14/01/2010